SYNTHESIS OF SUBSTITUTED 4H-IMIDAZO[1,5-*a*]BENZIMIDAZOLES

VIII.* SYNTHESIS OF 1-PHENYL-4-BENZYLIMIDAZO[1,5-*a*]BENZIMIDAZOLE AND SOME 3-SUBSTITUTED DERIVATIVES

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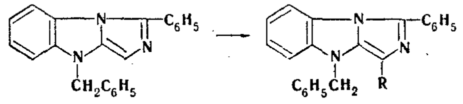
1-Phenyl-4-benzylimidazo[1,5-*a*]benzimidazole (III) was synthesized and subjected to acetylation, azo coupling, and the Vilsmeier reaction at the 3 position. 1-Phenyl-3-cyano-4-benzylimidazo[1,5-*a*]benzimidazole (X) was also obtained.

We have previously [2] described the synthesis and several substitution reactions of 4-methylimidazo[1,5-*a*]benzimidazole derivatives that do not have substituents in the 3 position. In a continuation of this study, 1-benzyl-2-benzamidomethylbenzimidazole (II) was synthesized via the scheme described for the preparation of 1-phenyl-4-methylimidazo[1,5-*a*]benzimidazole (I) [2] from N-benzyl-o-phenylenediamine and ethyl hippurate; II was then converted to 1-phenyl-4-benzylimidazo[1,5-*a*]benzimidazole (III). The structure of III was confirmed by the spectral data. The IR spectrum of III does not contain the absorption bands of the CO and NH groups, which are present in the IR spectrum of II, and intense splitting, which is characteristic for these three-ring compounds, of the absorption band at 1594 and 1615 cm^{-1} is observed. The UV spectrum of III differs sharply from the UV spectrum of II and coincides with the UV spectrum of I [2]. The signal of the proton attached to the carbon atom in the 3 position and the signal of the protons of the NCH_2 group (singlets at 6.42 and 5.09 ppm, respectively) are distinctly seen in the PMR spectrum.† In contrast to I, III is stable to light in the presence of air oxygen.

Acetylation of III with acetic anhydride in the presence of anhydrous sodium acetate gives 1-phenyl-3-acetyl-4-benzylimidazo[1,5-*a*]benzimidazole (IV) in high yield. The UV spectrum of IV coincides completely with that of the 3-acetyl derivative of I [2].

Azo coupling of III was carried out with p-bromo- and p-methoxybenzenediazonium fluoborates as previously described for the synthesis of 1-(p-methoxyphenylazo)-3-phenyl-4-methylimidazo[1,5-*a*]benzimidazole [3]. The products of azo coupling were isolated from the reaction mass as the hydrofluoborates, from which the corresponding bases – 1-(p-bromophenylazo)- (V) and 1-(p-methoxyphenylazo)-4-benzylimidazo[1,5-*a*]benzimidazole (VI), respectively – were obtained after heating the salts in dimethylformamide–water.



III IV-X

IV $R=COCH_3$; V $R=p\text{-}BrC_6H_4N_2$; VI $R=p\text{-}CH_3OC_6H_4N_2$; VII $R=CHO$;
VIII $R=CH{=}NNHCSNH_2$; IX $R=CH{=}NOH$; X $R=CN$

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* See [1] for communication VII. This system was designated 4H-imidazo[5,1-b]benzimidazole in the preceding communications of this series.

† The signals of the aromatic protons form a complex multiplet from which the chemical shifts cannot be determined without special analysis.

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The Vilsmeier reaction was carried out under the conditions described for the preparation of 3-phenyl-4-methyl- [4] and 3,4-dimethylimidazo[1,5-*a*]-1-formylbenzimidazoles [1]. However, 1-phenyl-4-benzylimidazo[1,5-*a*]-3-formylbenzimidazole (VII) was isolated from the reaction mass only after treatment of it with 10% sodium hydroxide solution. The PMR spectrum of VII does not contain the signal of a proton attached to the carbon atom in the 3 position, but the signal of the proton of an aldehyde group (singlet at 9.84 ppm) is observed.

The thiosemicarbazone (VIII) and oxime (IX) were obtained from VII by the usual methods. The latter was converted to the nitrile, the IR spectrum of which contains an absorption band characteristic for the CN group (2210 cm^{-1}). The starting material was recovered in an attempt to obtain the thioamide by passing hydrogen sulfide into a suspension of X in ethanol in the presence of triethylamine at 20°.

EXPERIMENTAL

1-Benzyl-2-benzamidomethylbenzimidazole (II). A mixture of 6.61 g (33.5 mmole) of N-benzyl-o-phenylenediamine and 6.91 g (33.5 mmole) of ethyl hippurate was heated with stirring in a stream of nitrogen at 200° for 3.5 h, after which it was cooled, and the melt was triturated with ether. The solid was removed by filtration to give 6.48 g (56.6%) of II as long white needles with mp 182-183° (from ethanol). The product was readily soluble in chloroform, less soluble in benzene and ethyl acetate, and insoluble in water. IR spectrum: ν_{NH} 3320 cm^{-1}, ν_{CO} 1640 cm^{-1}. UV spectrum, λ_{max}, nm (log ε): 224 (4.26),* 246 (4.12),* 270 (3.86), 277 (3.91), 284 (3.82). Found: C 77.6; H 5.5; N 12.5%. $C_{22}H_{19}N_3O$. Calculated: C 77.4; H 5.6; N 12.3%.

1-Phenyl-4-benzylimidazo[1,5-*a*]benzimidazole (III). A suspension of 8.38 g (24.6 mmole) of II in 100 ml of anhydrous benzene and 23.8 ml of phosphorus oxychloride was refluxed until hydrogen chloride evolution ceased completely (~ 35 h). The benzene and excess phosphorus oxychloride were removed by vacuum distillation, and the residue was made alkaline with a saturated solution of $NaHCO_3$. The precipitate was removed by filtration, washed with water, and dried to give 7.36 g (93%) of III as a light-yellow crystalline substance with mp 147.5-150° (from absolute ethanol). The product was readily soluble in alcohol, ethyl acetate, and benzene, less soluble in ether, and insoluble in water. UV spectrum, λ_{max}, nm (log ε): 230 (4.22),* 251 (4.02),* 281 (4.05), 351 (4.18). PMR spectrum, δ, ppm: singlets at 6.42 (3-H) and 5.09 (NCH_2). Found: C 81.3; H 5.1; N 13.1%. $C_{22}H_{17}N_3$. Calculated: C 81.7; H 5.3; N 13.0%.

1-Phenyl-3-acetyl-4-benzylimidazo[1,5-*a*]benzimidazole (IV). A mixture of 0.37 g (1.15 mmole) of III, 0.26 g (3.17 mmole) of anhydrous sodium acetate, and 2.4 ml (25.5 mmole) of acetic anhydride was heated at 90-100° for 1.5 h and at 120° for 30 min, after which it was vacuum-evaporated, and the residue was triturated with water. The solid was removed by filtration to give 0.4 g (96%) of IV as shiny long gray needles with mp 182-183° (from absolute ethanol). The product was readily soluble in the cold in chloroform, benzene, and ethyl acetate, less soluble in ether, and insoluble in water and hexane. IR spectrum: ν_{CO} 1640 cm^{-1}. UV spectrum, λ_{max}, nm (log ε): 225 (4.36), 328 (4.52). PMR spectrum, δ, ppm: singlets at 2.70 ($COCH_3$), 6.13 (NCH_2). Found: C 79.0; H 5.5; N 11.7%. $C_{24}H_{19}N_3O$. Calculated: C 78.9; H 5.3; N 11.5%.

1-Phenyl-3-(p-bromophenylazo)-4-benzylimidazo[1,5-*a*]benzimidazole (V). A suspension of 0.34 g (1.49 mmole) of p-bromobenzenediazonium fluoborate in 6 ml of methanol and 0.6 ml of acetic anhydride was added at 20° to a solution of 0.43 g (1.33 mmole) of III and 0.25 g (3.05 mmole) of anhydrous sodium acetate in 6 ml of acetic acid and 1.3 ml (13.8 mmole) of acetic anhydride, after which the mixture was allowed to stand in a dark place for 7 days. The precipitate (0.48 g) was removed by filtration, washed with ether, and dissolved by heating in the minimum amount of DMF. Water was then added to the aqueous solution until an amorphous precipitate appeared. The latter was redissolved by heating while adding DMF dropwise, and the solution was filtered. The precipitated bright-orange needles were removed by filtration and washed initially with a small amount of DMF–water (1 : 1) and then ether to give 0.31 g (46%) of V with mp 221-223°. The product was readily soluble in methanol. Found: C 66.6; H 3.8; Br 16.0; N13.6%. $C_{23}H_{20}BrN_5$. Calculated: C 66.4; H 4.0; Br 15.8; N 13.8%.

1-Phenyl-3-(p-methoxyphenylazo)-4-benzylimidazo[1,5-*a*]benzimidazole (VI). This compound (29.7%), with mp 183-184°, was similarly obtained from III and p-methoxybenzenediazonium fluoborate. The dark-orange needles were readily soluble in methanol. Found: C 76.0; H 5.3; N 15.0%. $C_{29}H_{23}N_5O$. Calculated: C 76.1; H 5.1; N 15.3%.

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* Inflection. The inflections in the UV spectra will subsequently be designated by an asterisk.

1-Phenyl-4-benzylimidazo[1,5-*a*]-3-formylbenzimidazole (VII). A 2.4-ml (26.7 mmole) sample of $POCl_3$ was added dropwise to 14 ml of purified and freshly distilled DMF cooled to 0°, and the mixture was stirred at 20° for 15 min. It was then cooled to 0°, and a solution of 3.12 g (9.65 mmole) of III in 30 ml of DMF was added. The mixture was then stirred for 4 h and allowed to stand for 12 h, after which it was poured over ice and carefully made alkaline to pH 8 with 10% sodium hydroxide. The precipitate was removed by filtration, washed with water, and dried to give 3.38 g (99.5%) of crystalline VII with mp 190-192° (from 50% ethanol). The product was readily soluble in the cold in chloroform and benzene, less soluble in ethyl acetate, and only slightly soluble in ether. IR spectrum: ν_{CO} 1650, 1662 cm^{-1}. UV spectrum, λ_{max}, nm (log ε): (CHO).[†] Found: C 78.6; H 4.9; N 11.8%. $C_{23}H_{17}N_3O$. Calculated: C 78.6; H 4.9; N 12.0%.

1-Phenyl-4-benzylimidazo[1,5-*a*]-3-formylbenzimidazole Thiosemicarbazone (VIII). A suspension of 0.5 g (1.43 mmole) of VII, 0.14 g (1.53 mmole) of thiosemicarbazide, 11 ml of absolute ethanol, and 1.5 ml of acetic acid was refluxed for 3 h, during which VII gradually dissolved. The precipitate that appeared after 1 h was removed from the cooled mixture by filtration and washed successively with ethanol and ether to give 0.48 g (79.5%) of fine light-yellow needles of VIII with mp 225.5-227.5° (dec.) after recrystallization, initially from acetic acid and then from a large amount of absolute ethanol. Found: C 68.0; H 4.9; N 19.5; S 7.3%. $C_{24}H_{20}N_6S$. Calculated: C 67.9; H 4.8; N 19.8; S 7.6%.

1-Phenyl-4-benzylimidazo[1,5-*a*]-3-formylbenzimidazole Oxime (IX). A mixture of 2 g (5.7 mmole) of VII, 2 g of hydroxylamine hydrochloride, 10 ml of absolute ethanol, and 10 ml of anhydrous pyridine was heated at 100° for 3 h, after which the mixture was evaporated and the residue was treated with water. The resulting solid was removed by filtration to give 2 g (96%) of white crystalline IX with mp 191-193° (from absolute ethanol). Found: C 75.6; H 4.8; N 15.0%. $C_{23}H_{18}N_4O$. Calculated: C 75.4; H 5.0; N 15.3%.

1-Phenyl-3-cyano-4-benzylimidazo[1,5-*a*]benzimidazole (X). A mixture of 1.5 g (4.12 mmole) of IX, 0.47 g (5.75 mmole) of anhydrous sodium acetate, and 14 ml of acetic anhydride was refluxed for 3 h, after which it was vacuum-evaporated, and the residue was treated with water. The solid was removed by filtration to give 1.3 g (91%) of rose-colored needles of X with mp 204.5-206° (after successive recrystallization from butanol and acetic acid). IR spectrum: ν_{CN} 2200 cm^{-1}. UV spectrum: λ_{max}, nm (log ε): 232 (4.30), 280 (4.34), 327 (4.12). Found: C 79.2; H 4.6; N 16.1%. $C_{23}H_{26}N_4$. Calculated: C 79.3; H 4.6; N 16.1%.

The UV spectra of alcohol solutions of the compounds were recorded with SF-4 and EPS-3 spectrophotometers. The PMR spectra of $CDCl_3$ solutions were recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz with tetramethylsilane as the internal standard. The IR spectra were recorded with a UR-10 recording spectrophotometer.

LITERATURE CITED

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[†] As in Russian original – Publisher.